

NARRATIVE REVIEW



Physiological determinants and the red blood cells transfusion decision-making process in non-bleeding critically ill patients: a comprehensive narrative review

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Abstract

Purpose: There is a willingness to move towards a more personalised medicine; however, the red blood cells' (RBC) transfusion decision-making process remains a one-size-fits-all practice in most non-bleeding critically ill patients. This narrative review describes the limitations of a transfusion decision-making process based only on haemoglobin (Hb) threshold and the potential physiological triggers of RBC transfusion with the clinical evidence investigating their implementation in routine.

Results: Hb does not reflect tissue oxygenation and anaemia tolerance, and applying the same Hb threshold throughout the ICU stay neither prevents unnecessary transfusion nor insufficient transfusion. Central venous oxygen saturation (ScvO₂) and oxygen extraction ratio (O₂ER) are accessible at the bedside and display significant changes after RBC transfusion when in abnormal ranges. Although they have been prospectively investigated in the transfusion decision process, there is a need for more evidence to definitely implement them in routine. The arterial–venous difference in oxygen (A–VO_{2diff}) might be another useful bedside RBC transfusion trigger. Microcirculatory markers are also promising candidates for physiological determinants for RBC transfusion.

Conclusions: There is a need for additional determinants in the RBC transfusion decision process to offset the limitations of RBC transfusion based only on Hb level in non-bleeding critically ill patients. A multimodal strategy, including comorbidities, underlying diseases, clinical signs, ECG changes, biochemical markers, and microcirculatory assessment, may optimise transfusion timing and avoid unnecessary red blood cell administration. However, further research is warranted to determine the potential benefit of integrating tissue oxygenation and microcirculatory parameters in the transfusion decision-making process.

Keywords: Red blood cell, Critically ill patients, Transfusion decision, Physiological triggers, ScvO₂, O₂ER, Microcirculation

Background

More than 45 randomised-controlled trials have investigated the optimal haemoglobin (Hb) thresholds for red blood cell (RBC) transfusion in patients of different settings, including critical care, cardiac and non-cardiac post-surgery, and onco-haematology [1, 2]. Most of those trials have reported a non-inferiority in mortality and/or morbidity in patients transfused with a low or

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“restrictive” Hb threshold (usually between 7 and 8 g/dL) in comparison with a high or “liberal” Hb threshold (usually between 9 and 10 g/dL). The restrictive transfusion strategy is also associated with a decrease in the number of patients transfused and a decrease in the number of RBC transfused per patient and overall [1, 2]. Based on this evidence, guidelines recommend a restrictive transfusion strategy unless specific settings, including patient with acute coronary syndrome [1, 3]. More recently, the TOP randomised trial compared two RBC transfusion strategies in post-operative patients at high cardiac risk and did not find any difference in the composite primary outcome (i.e. all-cause death, myocardial infarction, coronary revascularization, acute kidney failure, or ischaemic stroke). Based on these results, a Hb threshold of 7 g/dL would also be appropriate in post-operative patients with stabilised cardiovascular status [4].

However, guidelines also highlighted the need to integrate other determinants than Hb concentrations in the decision to transfuse RBC in non-bleeding critically ill patients [2, 3]. Both the European guidelines for transfusion in non-bleeding critically ill patients and the most recent American Association of Blood Banks (AABB) guidelines emphasised the importance of accounting for anaemia tolerance when making transfusion decisions in this population [2, 3]. Similarly, experts have refrained from recommending a specific Hb threshold in the context of post-cardiac surgery rehabilitation, reflecting a shift towards more individualised RBC transfusion practices [5]. There is also an increasing interest for functional outcomes; in a large randomised-controlled trial comparing two transfusion strategies in patients undergoing hip replacement, the inability to walk across a room without human assistance was integrated in the primary outcome [6]. In another trial evaluating anaemic women after post-partum haemorrhage, physical fatigue and health-related quality of life were considered as main outcomes [7]. Although none of those both trials found a difference in functional outcomes between patients receiving one or the other transfusion strategy, improvement in the mean walk test distance after RBC transfusion has been reported in anaemic cancer patients [8].

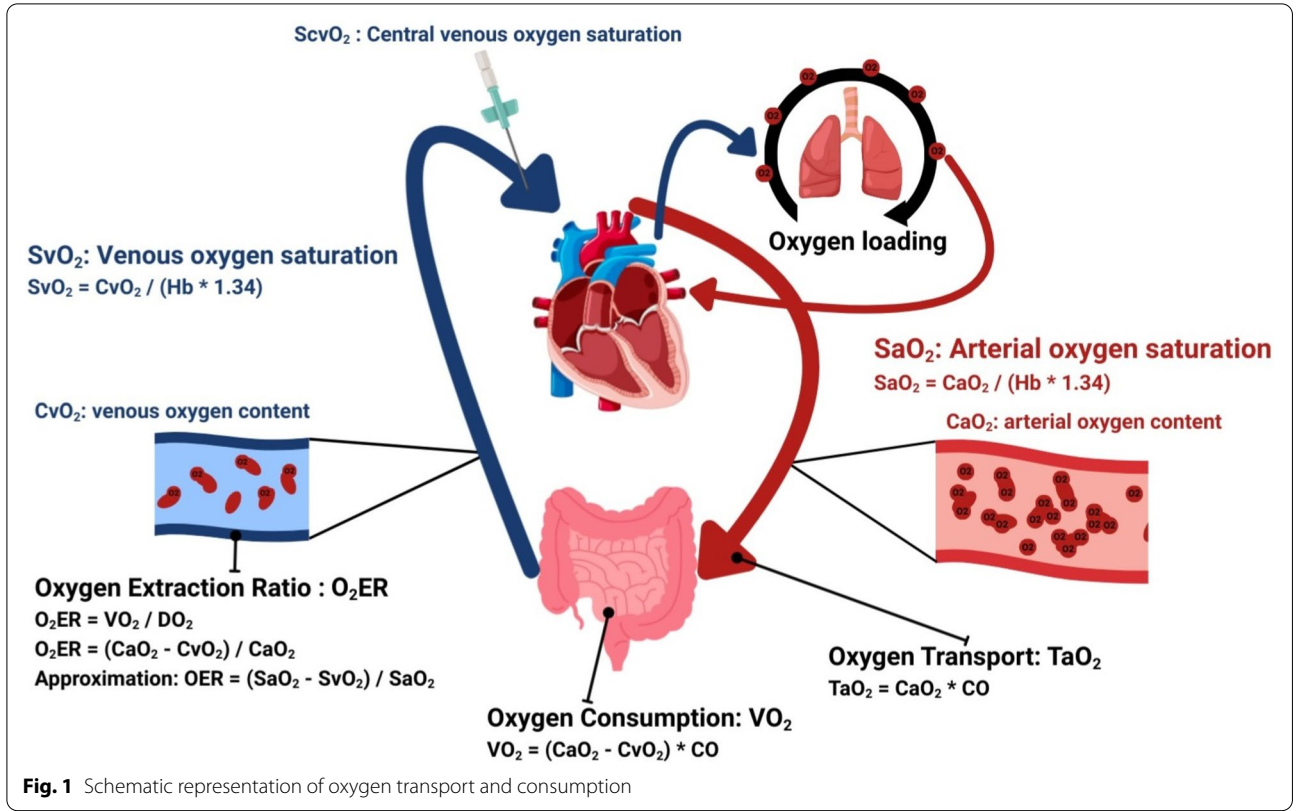
Additional transfusion determinants have recently been reported as part of the transfusion decision-making process. In the TRACE online survey, more than half of the 725 respondents indicated that they always or often relied on specific physiological triggers, the most common being tachycardia (66%), hypotension (55%), and lactate levels exceeding 2 mmol/L (51%) [5]. In the international prospective INPUT cohort study, which included 3,643 patients across 233 ICUs between 2019 and 2022, RBC transfusion was predominantly guided by a low Hb value (mean lowest Hb: 7.4 g/dL—81.8%),

haemodynamic instability (23.5%), and active bleeding (27.5%) [9]. Amongst the physiological triggers evaluated in this study, the most frequently used were hypotension (42.2%), tachycardia (27.4%), and elevated lactate levels (17.8%) [9]. Conversely, central venous oxygen saturation ($ScvO_2$) < 65% and electrocardiogram (ECG) changes contributed to transfusion decisions in only 36 (2%) and 23 (1%) transfusion events, respectively. A recent systematic review suggested that monitoring tissue oxygenation and microcirculatory parameters may provide a more effective approach to guide RBC transfusion in critically ill patients than relying solely on Hb thresholds [10].

Advancing towards more individualised transfusion practices requires validated tools to better identify situations in routine care where the benefits of transfusion outweigh the risks associated with both RBC transfusion and anaemia. This narrative review aims: (1) to summarise the key elements of oxygen (O_2) transport and tissue oxygenation; (2) to explain why RBC transfusion decision based only on Hb level might be unsuitable; and (3) to describe potential candidates of physiological triggers for RBC transfusion and introduce the clinically available evidence to support their use in the RBC transfusion decision-making process.

Oxygen transport, oxygen consumption, and adaptation mechanisms to a drop in Hb

Oxygen transport, defined as O_2 going from the pulmonary alveoli into the arterioles and O_2 delivery, defined to O_2 going from the pulmonary alveoli to the tissues and cells, relies on the “oxygen cascade” that corresponds to the passive transfer of O_2 through a pressure gradient from the atmosphere through lung alveoli and ultimately to the mitochondria as well as the active transport of oxygen bound to Hb within erythrocytes, carried via cardiac output (CO) from the alveoli to peripheral tissues [11, 12]. In this process, Hb is transported via larger vessels within the systemic circulation and delivers oxygen to the tissues through the microvascular network (Fig. 1) [12, 13]. Oxygen delivery (DO_2) is the rate of O_2 delivered to the tissues and mainly depends on four parameters including CO, Hb level, Hb saturation in oxygen and microcirculatory function [13]. Indeed, O_2 binds at 98–99% to the Hb, with 1 g of Hb carrying 1.34 mL of O_2 . A negligible part of O_2 is dissolved in blood, depending of the arterial partial pressure in O_2 and of O_2 solubility coefficient ($0.003 \times PaO_2$). As a result, arterial O_2 content (CaO_2) is mainly O_2 bound to Hb and can be assessed by the following equation: $CaO_2 = 1.34 \times Hb \times SaO_2$, with SaO_2 being the arterial saturation in oxygen. Oxygen transport (TaO_2) is equal to arterial O_2 content (CaO_2) by the CO [14, 15] (Fig. 1)



$$TaO_2 = CaO_2 \times CO.$$

Based on the O₂ arterial content formula, TaO₂ can also be expressed as follows [15, 16]:

$$TaO_2 = ((Hb \times 1.34 \times SaO_2) + (0.0031 \times PaO_2)) \times CO.$$

VO₂ is defined as the rate of oxygen uptake into the tissues ($VO_2 = CO (CaO_2 - CvO_2)$). In physiological conditions and at rest, DO₂ largely covers oxygen consumption (VO₂) [17, 18]. When DO₂/VO₂ ratio decreases, either because of a decrease in DO₂ or an increase in VO₂ or both, and when compensatory mechanisms are insufficient to offset these changes, the VO₂ decreases, aerobic metabolism switches to anaerobic metabolism, leading to a decrease in ATP production, increased production of lactate, acidemia, and possibly cell death through different mechanisms, including mainly necrosis and apoptosis (Fig. 2) [19].

In case of euvolemic anaemia, compensatory mechanisms aiming to maintain adequate DO₂ and aerobic cellular metabolism include increased sympathetic tone (e.g., resulting in tachycardia and enhanced cardiac contractility), decreased vascular resistance (e.g., because of reduced shear stress), and blood viscosity, also leading to higher CO [20, 21]. Another adaptive response to a drop in DO₂ is the increase in systemic oxygen

extraction ratio (O₂ER) (Fig. 2). In baseline conditions, 20–30% of O₂ bound to Hb is extracted by the tissues; thus, enhancing O₂ER helps maintaining the independence of VO₂ from DO₂. Higher O₂ER will lead to a drop in venous O₂ saturation (SvO₂) and content (CvO₂, with $CvO_2 = Hb \times 1.34 \times SvO_2$). Oxygen extraction can be estimated from the arterio-venous difference in O₂

$$O_2 ER = \frac{(CaO_2 - CvO_2) \times CO}{CaO_2 \times CO}.$$

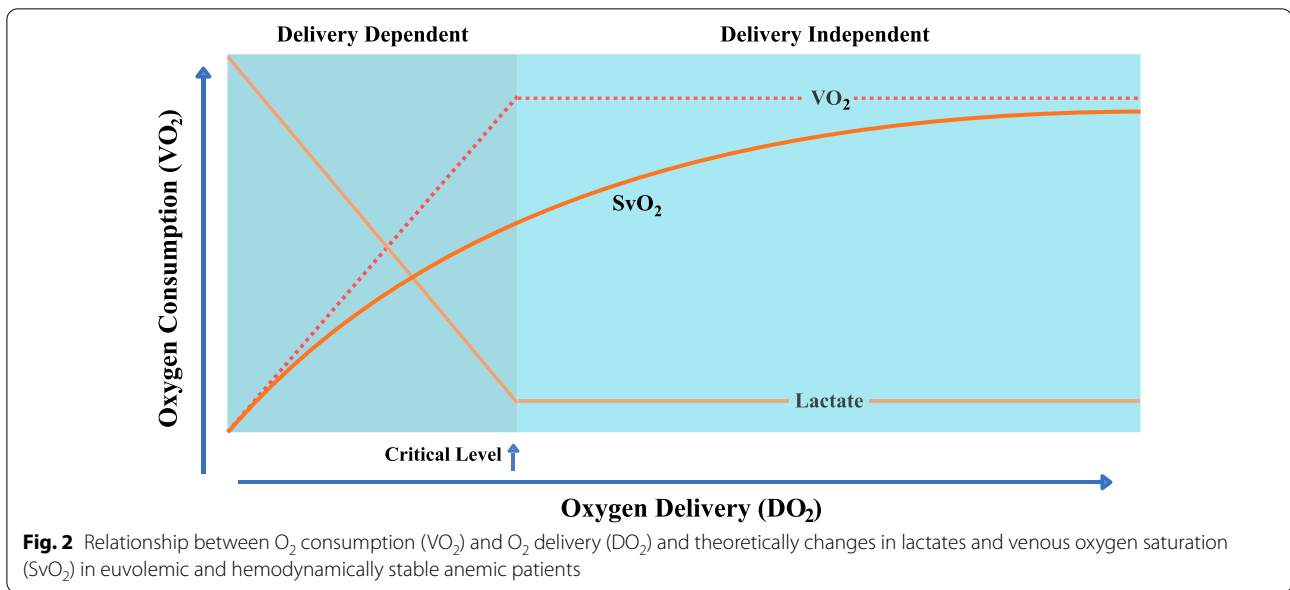
This equation can also be written as [15, 16]

$$O_2 ER = \frac{(CaO_2 - CvO_2)}{CaO_2} = \frac{(SaO_2 - SvO_2)}{SaO_2}.$$

As a consequence, SvO₂ is as follows:

$$SvO_2 = SaO_2 - \left[\frac{VO_2}{CO \times Hb \times 1.34} \right].$$

Under normal baseline conditions, the SvO₂ values range between 70 and 75%. Venous oxygen content and SvO₂ can be considered as surrogates of oxygen reserve, O₂ER being not available in routine. However, SvO₂ is measured directly in the pulmonary artery and requires a pulmonary artery catheter, whilst the central venous oxygen saturation (ScvO₂) can be obtained from the



superior vena cava and mainly represents O_2 ER from the upper body (i.e., brain and the upper extremities). There is a good correlation between $ScvO_2$ and SvO_2 , although $ScvO_2$ is slightly higher than SvO_2 and may underestimate splanchnic hypoperfusion [22–24]. This is particularly relevant in patients with shock, in whom $ScvO_2$ is often significantly greater than SvO_2 , as splanchnic hypoperfusion is frequent finding in this setting [25]. A drop in SvO_2 and/or $ScvO_2$ might reflect an unbalance between DO_2 and VO_2 , as a greater fraction of the delivered oxygen is utilised by the tissues; however, a reduction in SvO_2 and/or $ScvO_2$ is not, in itself, a marker of tissue hypoxia or anaerobic metabolism; rather, it reflects an increase in oxygen extraction regardless of tissue tolerance.

In this context, monitoring of carbon dioxide (CO_2) production (VCO_2) might add useful information. When the body CO_2 and O_2 pools are in a steady state, the VCO_2 and VO_2 measurements can be used to assess cellular metabolism [26, 27]. Under aerobic conditions, both VO_2 and VCO_2 depend primarily on the metabolic activity of the tissues. The relationship between VO_2 and VCO_2 during aerobic metabolism is expressed as the respiratory quotient ($RQ = VCO_2/VO_2$), which provides a dynamic, integrative metric of substrate utilisation at the cellular level and depends on the predominant oxidised substrate (glucose, $RQ = 1$; proteins, $RQ = 0.8$; lipids, $RQ = 0.7$, which is around 0.8 in a mixed diet). A high RQ (> 1), as seen with predominant carbohydrate metabolism or anaerobic CO_2 production, may indicate preserved mitochondrial function associated with either insufficient DO_2 , as in early circulatory failure (e.g. low SvO_2), or

microvascular failure (e.g. high SvO_2). Conversely, a low RQ (< 0.7), typical of fat oxidation, requires more oxygen for the same energy yield, increasing VO_2 and potentially lowering SvO_2 (e.g., fasting or malnutrition), even in the absence of hypoxia. As the RQ is difficult to assess in clinical practice, the veno-arterial CO_2 difference or gap ($Pv-aCO_2$) is often used at the bedside as a surrogate, as it reflects the balance between CO_2 production and clearance, rising in low cardiac output states due to stagnant tissue perfusion. Whilst it serves as a sensitive marker for hypoperfusion, it does not reliably increase in hypoxic, anaemic, or cytopathic dysoxia. As such, a combination of $SvO_2/ScvO_2$ and $Pv-aCO_2$ would be useful in assessing perfusion adequacy and tissue hypoperfusion [26].

Microcirculation is the terminal vascular network responsible for distributing RBCs to tissues and is therefore central to maintaining adequate oxygenation [13]. In anaemia, adaptive microcirculatory responses, such as increased capillary recruitment, more homogeneous RBC flow patterns, reduced diffusion distance, and increased flow velocity due to lower viscosity, help preserve tissue oxygen delivery as a compensatory mechanism to mitigate tissue hypoxia [28, 29] [30, 31]. Given that Hb is a key determinant of oxygen availability, preserving the mechanisms of oxygen transport in the microcirculation (tissue perfusion and diffusion) is essential to ensure that an adequate number of RBCs reach the microcirculation to increase the oxygen-carrying capacity of the blood, and maintain sufficient tissue oxygenation to meet tissue metabolic demands [13]. Accordingly, microcirculatory parameters may serve as surrogate markers of tissue DO_2 .

Why should RBC transfusion not be based only on haemoglobin in critically ill patients?

There are several reasons supporting the idea that transfusion decisions should not be based solely on Hb levels (Fig. 3). First, anaemia tolerance in critically ill patients is difficult to predict, and Hb level does not reflect it. Tachycardia is common in intensive care unit (ICU) patients and is likely to be multifactorial, making it difficult to relate it to anaemia. An increase in CO leads to higher myocardial oxygen demand and might then result in type 2 myocardial infarction in patients with underlying cardiovascular diseases or cardiovascular risk factors. Assessing anaemia cardiac tolerance in the setting of critical care is uneasy as more than half of ICU patients require invasive mechanical ventilation and sedation during their ICU stay, and as changes in ECG or troponin concentrations are neither systematically monitored nor specific [32]. As a consequence, in a meta-analysis on transfusion strategies in patients with cardiovascular disease, Docherty et al. reported that only 7 of the 11 included trials clearly defined myocardial infarction, and only 4 had

a specific algorithm to diagnose myocardial infarction in the study groups [33]. In the same way, dyspnoea cannot be linked to a Hb decrease in critically ill patients as this is a very common symptom and only evaluable in non-sedated patients.

Second, applying the same Hb threshold for RBC transfusion throughout the ICU stay neither prevents unnecessary transfusions nor ensures that transfusion is adequate when required. Studies investigating the optimal transfusion strategy in critically ill patients compared most often the same strategy in subgroups of patients defined mainly by their baseline characteristics including the reason for ICU admission (e.g., septic shock or trauma brain injury) or their medical past history (e.g., cardiovascular disease and oncology), without considering the physio-pathological state changes along the ICU stay [34]. The same Hb threshold might be optimal at one stage of the critical illness and inadequate at another stage, as oxygen needs vary with the clinical and physiological conditions. Typically, conditions associated with higher VO_2 include fever, physical rehabilitation

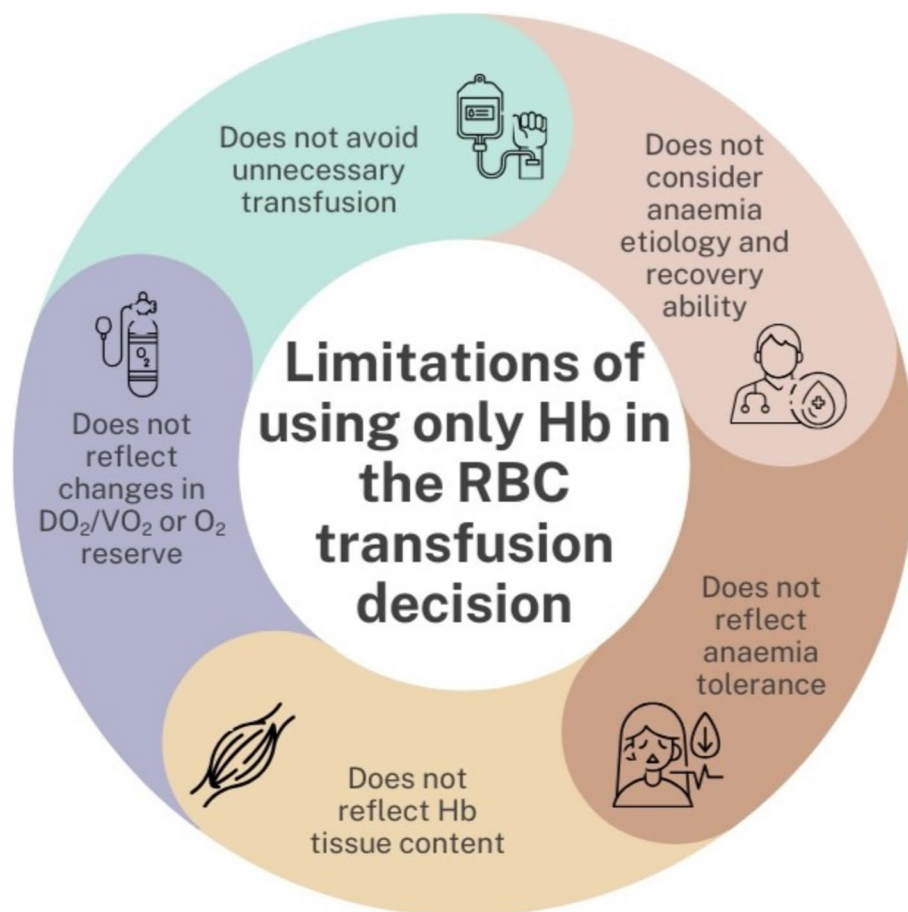


Fig. 3 Limitations of a transfusion decision-making process based only on Hb (haemoglobin) level

with exercise and mobilisation, and ventilation weaning, whilst those associated with decreased VO_2 include sedation, hypothermia, and mechanical ventilation [19]. In the landmark study on the Hb threshold for RBC transfusion, performed by Hebert et al., the less severe patients who had a Simplified Acute Physiology Score II less than 50 had a higher mortality when transfused according to a liberal transfusion strategy than patients transfused with a restrictive strategy [34]. This finding suggests that a study applying the same Hb threshold might fail to demonstrate any benefit of higher or lower thresholds, because an intervention that is beneficial at one moment might be deleterious at another, when the physio-pathological state and oxygen needs have changed. They also emphasise that unnecessary RBC transfusion might be deleterious, as discussed below [34].

Third, transfusion decisions must consider that allogeneic RBC transfusion is associated with a range of potential adverse effects. Using Hb concentrations alone as the trigger and/or target for transfusion fails to account for the morbidity linked to RBC administration. Although some complications with clear causal pathways are well recognised, such as haemolytic reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO) [35], RBC transfusion has also been associated with broader clinical harms. These include an increased risk of health-care-associated infections and neurological complications [36, 37], even though transfusion thresholds have varied across studies and modern blood management practices likely reduce the frequency of such events compared with trials conducted more than a decade ago. Taken together, these considerations emphasise two urgent priorities: (a) RBC transfusion should be restricted to situations in which it is clearly necessary, and (b) further research is needed to better characterise the risks and mechanisms of transfusion-related adverse events, particularly within contemporary transfusion practices.

Fourth, Hb does not reflect the oxygen reserve nor the DO_2/VO_2 . In a healthy resting person, the DO_2/VO_2 is equal to 5:1, leaving the possibility to fulfil the demand in case of an increase in VO_2 (for instance, during physical efforts). In patients with decreased DO_2 secondary to a drop in Hb, ageing, or an underlying coronaropathy, an increase in VO_2 might lead to anaerobic metabolism because of reduced compensatory mechanisms. The critical DO_2 is the DO_2 below which cell metabolism switches to this anaerobic metabolism leading to tissue hypoxia and organ failure. The critical DO_2 is likely to be different between patients and between organs. Delay in RBC transfusion may expose patient to the risk of tissue hypoxia on the one hand and prevent transfusion-related morbidity on the other hand. Although there is no clearly

defined Hb threshold below which mortality or complications risk increases, studies conducted in patients refusing RBC transfusion for religious reasons reported a higher occurrence of acute myocardial infarction and infection, when Hb dropped below 8 g/dL [38, 39]. In a cohort of 300 patients with a post-operative anaemia (i.e. Hb of 8 g/dL or less) who declined RBC transfusion, mortality increased when Hb dropped; however, patients with a post-operative Hb nadir between 6 and 7 g/dL had similar mortality rates than those with Hb between 5 and 6 g/dL [38].

Studies performed in resting healthy volunteers found almost no change in DO_2 when Hb dropped up to 4.8 g/dL. However, these findings cannot be directly extrapolated to critically ill patients. Studies performed in healthy volunteers do not account for the profound pathophysiological alterations that accompany critical illness, nor do they address the tolerance of prolonged anaemia or the impact of anaemia on organ-specific dysfunction [39, 40]. Although lowering the Hb threshold below 7 g/dL may be feasible in selected patients, such an approach requires rigorous investigation and careful monitoring of organ tolerance, particularly with respect to cardiac, neurological and renal function. A pilot randomised trial comparing two transfusion thresholds (5 g/dL vs. 7 g/dL) is currently underway [41], and its findings will be critical to better define the safety and physiological consequences of ultra-restrictive transfusion strategies in the ICU.

Finally, systemic Hb levels may not accurately reflect tissue Hb content, as microvascular haematocrit (Htc) is often lower than that in the larger vessels [42–45]. This discrepancy arises from heterogeneous flow distribution, the Fahraeus effect, and the Zweifach–Fung effect; the Fahraeus effect is the reduction in the apparent haematocrit (red blood cell concentration) of blood as it flows through small-diameter capillaries compared to larger vessels. It occurs, because RBCs tend to travel faster than plasma in microvessels, leading to a lower cell-to-plasma ratio in the capillary blood. The Zweifach–Fung effect refers to the uneven distribution of RBCs at microvascular bifurcations, where one daughter vessel—typically one with lower flow—receives a disproportionately smaller share of RBCs compared to plasma, whilst the other branch receives a higher RBC concentration [44, 46]. Consequently, DO_2 at the tissue level may differ significantly from values inferred from the systemic circulation, where blood samples are typically obtained. This limitation renders systemic Hb a poor surrogate for estimating tissue perfusion or oxygenation in critically ill patients [44, 47].

The reasons for anaemia should also be considered in the transfusion decision. Hb level does not preclude the

ability and the delay to recover from anaemia. A drop in Hb secondary to acute but resolved gastrointestinal bleeding in a previously healthy patient can be corrected by iron administration, whilst prolonged systemic inflammation secondary to critical illness would hamper prompt anaemia recovery. The underlying causes of Hb decline must be carefully evaluated, as the management of anaemia due to acute massive bleeding differs substantially from the management of anaemia unrelated to bleeding [3, 48]. In the context of major haemorrhage, the Hb concentration does not fall immediately, because RBC and plasma are lost proportionally in the early phase. Consequently, Hb does not accurately reflect the initial severity of blood loss, and a measurable decline typically appears only after redistribution of extracellular fluid or administration of intra-venous fluids. For this reason, a normal or near-normal Hb level in the early stages of acute bleeding should not be considered reassuring and must not delay the initiation of RBC transfusion when clinical signs indicate significant haemorrhage. Early resuscitation should therefore be guided by the overall haemodynamic and clinical picture, including shock indices, ongoing blood loss, and physiological markers of tissue hypoperfusion, rather than Hb values alone.

Developing and validating additional triggers to integrate into the RBC transfusion decision-making process aim to offset some of the limitations of a decision based only on Hb. Given that the primary objective of RBC transfusion is to enhance tissue oxygen delivery, monitoring indices of tissue perfusion and oxygenation might help guide this intervention in critically ill patients [10]. Although restrictive transfusion strategies safely reduce unnecessary RBC administration without increasing mortality in large, heterogeneous ICU populations, an exclusively Hb-based approach is insufficient for individualised decision-making. Integrating physiological markers of oxygen delivery and tissue perfusion may allow clinicians to safely defer transfusion even when Hb falls below 7 g/dL, provided that organ function and global oxygenation remain adequate. Conversely, transfusion may be warranted despite Hb values above 7 g/dL, when there is evidence of impending or established tissue hypoxia. Thus, physiologically informed strategies, incorporating parameters such as central venous oxygen saturation, venous oxygen content, oxygen extraction ratio, microcirculatory indices, or organ-specific markers, may better prevent tissue ischaemia whilst minimising unnecessary RBC exposure.

What clinical evidence supports the use of physiological triggers for RBC transfusion?

To better personalise RBC transfusion beyond the use of Hb thresholds, physiological triggers reflecting O_2

reserve and anaemia tolerance might be useful and have been investigated. Amongst them, ScvO₂ provides a dynamic measure of the balance between oxygen delivery and consumption, assuming that the other determinants remain unchanged. Similarly, the arterial–venous O_2 difference ($A-VO_{2diff}$) could also serve as an index of tissue oxygenation. Increase in troponin levels can reflect an imbalance between oxygen supply and demand in the setting of anaemia. However, it remains unclear how to integrate these parameters in the RBC transfusion decision in ICU and whether their use benefits to patients. Besides these triggers, arterial lactate concentration is routinely used as a surrogate of tissue hypoxemia despite the lack of strong evidence supporting an association between RBC transfusion and changes in lactate concentration [10, 21]. Table 1 summarises the advantages and drawbacks of potential physiological triggers for RBC transfusion.

ScvO₂

ScvO₂ has been investigated both, as part of a bundle of resuscitation measures including RBC transfusion or as an isolated trigger for transfusion [49, 50]. In patients with sepsis and septic shock, the landmark study conducted by Rivers et al., more than 2 decades ago, compared the management of patients admitted to the emergency department with a 6-h protocol of early goal directed therapy (EGDT) that was based on a ScvO₂ > 70% achievement in comparison to standard of care [49]. In this single-centre randomised-controlled trial, patients in the EGDT group had a significantly lower 30-day mortality than those managed as per standard of care (30.5–46.5%, $p=0.009$) [49]. Although patients in the EGDT group received more than threefold RBC transfusion than those in the standard of care group, it was not possible to individualise the role played by RBC transfusion from the other interventions (i.e., fluid, vasopressors, or inotropes administration) on the observed effect. This study suffered important limitations, namely, single-centre and poor external validity, precluding any generalisation of its results. Further international multicentre randomised trials have investigated early septic shock management integrating ScvO₂ and its determinants [50–52]. These trials and an individual patient level meta-analysis did not find any difference in mortality between groups, whilst patients in the intervention group received around 5–7% more RBC transfusion [49–52]. Nonetheless, the EGDT did not really address the question of transfusion strategy based on ScvO₂ [49].

Several observational studies have analysed the changes in ScvO₂ after RBC transfusion in different settings (post-surgery, critical care, and neuro intensive care), to determine the best ScvO₂ cut off that would predict

Table 1 Advantages and drawbacks of potential physiological triggers for RBC transfusion

Potential physiological triggers	Advantages	Drawbacks
ScvO ₂	Reflects tissue oxygenation Easily measurable in ICU when superior cava venous CVC is inserted	Requires CVC in superior cava venous Does not only depend on Hb
Lactate	Easily measurable Might reflect tissue hypoxia	Not specific to anaemia Influenced by various factors (sepsis, medications, liver failure...)
SvO ₂ (SmvO ₂)	Strong reliability regarding tissular hypoxia	Requires pulmonary artery catheter (highly invasive) and does not only depend on Hb level
A-VO ₂ diff	Directly reflects tissue oxygen extraction	Requires arterial and venous blood gas measurements, influenced by cardiac output changes
O ₂ ER	Directly reflects balance between DO ₂ and VO ₂ Can detect impaired oxygen utilization even if DO ₂ is normal	Requires both arterial and central/mixed venous blood gas analyses Influenced by changes in metabolism and cardiac output
PtbO ₂	Reflects cerebral tissue oxygenation directly Associated with outcomes in acute brain injury	Requires invasive brain probe Only available in specialised neurocritical settings Inter-individual variability in response to transfusion
Tissue perfusion	Reflects tissue oxygen delivery Associated with outcomes in critically ill patients	Inter-individual variability in response to transfusion. Influenced by cardiac output changes. Only available in specialised settings ^a

ScvO₂ central venous oxygen saturation; CVC, central venous catheter; Hb, haemoglobin; A-VdiffO₂ Arterial-venous oxygen difference; O₂ER O₂ extraction ratio; PtbO₂ brain tissue oxygenation partial pressure; SvO₂ venous oxygen saturation; DO₂ oxygen delivery; VO₂ oxygen consumption

^a The techniques include NIRS (near-infrared spectroscopy), sublingual microcirculation, and laser Doppler

a response to RBC transfusion, commonly defined by a 5% change in ScvO₂ after transfusion (Supplemental Table 1). Adamczyk et al. found that only patients with a ScvO₂ value less than 70% had a significant change in ScvO₂ after RBC transfusion in a post-general surgery setting. The authors concluded that a ScvO₂ value of 70% had the best sensitivity (82%) and specificity (76%) to predict an increased ScvO₂ of at least 5% after transfusion, suggesting that anaemic patients with ScvO₂ higher than 70% would not benefit from RBC transfusion [53]. In a prospective observational study including 62 non-bleeding anaemic critically ill patients, ScvO₂ significantly increased after RBC administration (65% [IQR 59–73%] to 69% [62–75%], $p < 0.001$) [54]. Notably, only patients with ScvO₂ < 70% had a significant increase in ScvO₂ after RBC transfusion and a ScvO₂ less than 62.9% had the best sensitivity (61.1%) and the best specificity (76.5%) to predict an increase in ScvO₂ of at least 5% after RBC administration [54]. In this study, the 18 patients with altered cardiac function also had significant increase in ScvO₂ after transfusion, although the magnitude of this change might be clinically questionable (59.1% (50.1–71.1) to 61.8% (56.2–72.6%) $p = 0.02$). When analysed separately, patients with septic shock ($N = 32$) did not display any significant changes in ScvO₂ after RBC administration [54]. Some observational studies [55–57] had similar findings, whilst a large meta-analysis reported opposite results with changes in ScvO₂ (or SvO₂) after RBC transfusion reported in septic patients [21]. In 70 patients

admitted to neuro-ICU, the ScvO₂ changes after transfusion significantly correlated with pre-transfusion Hb and ScvO₂, as with the number of RBC units administered [58]. In this study, the cut offs that best predicted a 5% increase in ScvO₂ were ScvO₂ < 70% and an Hb less than 8.6 g/dL. Interestingly, ScvO₂ modifications persisted over 24 h after transfusion, suggesting a potential role on DO₂ independent from CO augmentation (e.g., increased preload) [58]. Indeed, ScvO₂ changes must be interpreted at the light of haemodynamic state and any correlation to the effect of anaemia/RBC transfusion should be done in hemodynamically stabilised patients [59].

Three randomised-controlled trials have compared a transfusion strategy based on Hb thresholds only to a strategy including ScvO₂ to the transfusion decision-making process in cardiac surgery patients (Supplemental Table 2). In a single-centre randomised-controlled trial including 100 patients, Zeroual et al. found that using a ScvO₂ < 65% compared to a Hb < 9 g/dL resulted in a 30% reduction in the number of transfused patients, without any significant difference in secondary outcomes [60]. Fischer et al. reported a reduction of the absolute risk of RBC transfusion by 21% (absolute risk – 21%, 95% confidence intervals – 32% to – 14%) when RBC transfusion was given only if ScvO₂ was < 70% compared to a transfusion strategy based on a Hb threshold of 9 g/dL; without any significant differences on other endpoints, including ischaemic events and mortality [61]. Recently, Saour et al.

compared transfusion exposure and clinical outcomes of patients transfused when Hb was less than 8 g/dL (control group) or when ScvO₂ was less than 65% and/or Hb less than 7 g/dL [62]. In the interventional group, anaemic patients also received intra-venous iron and erythropoietin. The interventions resulted in a decrease in 50% of transfused patients [62]. These three trials are interesting in their design and findings; however, they have relatively small sample sizes and are likely to be underpowered for crucial outcomes. Also, they focussed on hemodynamically stable patients after cardiac surgery, precluding any generalisation to other settings or to hemodynamically unstable patients. Finally, they report a decrease in the number of transfused patients; however, the Hb thresholds in the control group were relatively high and above the recommended standard of care [60, 61].

Arterial-venous O₂ difference

The A-VO_{2diff} is a surrogate of the DO₂/VO₂ ratio and has been proposed to identify patients who would and would not benefit from RBC transfusion [63]. Amongst 19 stable ICU patients, Schlager et al. did not find any significant change in A-VO_{2diff} between before and after RBC transfusion [64]. Amongst other observational studies in patients with and without sepsis, A-VO_{2diff} before and after transfusion varied from -0.17 to 0.70 mL/dL [65, 66]. A meta-analysis including 363 transfusions reported a significant increase in the mean A-VO_{2diff} of 0.13 (95% CI 0.01–0.24) after RBC transfusion, emphasising the impact of transfusion in oxygen delivery in non-bleeding critically ill patients [21]. In a prospective single-centre observational study including 177 anaemic non-bleeding critically ill patients, and where RBC were given based on Hb and clinical assessment, appropriate RBC transfusion strategy was defined as either an RBC transfusion given to patients with an A-VO_{2diff} higher than 3.7 mL, that was the median A-VO_{2diff} of the whole study population, or the absence of RBC transfusion in patients an A-VO_{2diff} lower or equal to 3.7 mL. Although, the Hb prior transfusion did not differ between groups, nor the transfusion rate, patients in the appropriate transfusion strategy group had a significantly lower 90-day mortality than those with an inappropriate transfusion strategy (23/96 patients [24%] vs. 36/81 patients [44%]; odds ratio [OR]=0.39 [95% CI 0.21–0.75], *p*=0.004) [63]. Additionally, organ function improved more rapidly in those patients with an appropriate transfusion strategy than in those with an inappropriate transfusion strategy [63]. Although these results require further investigations, the A-VO_{2diff} appears to be a promising

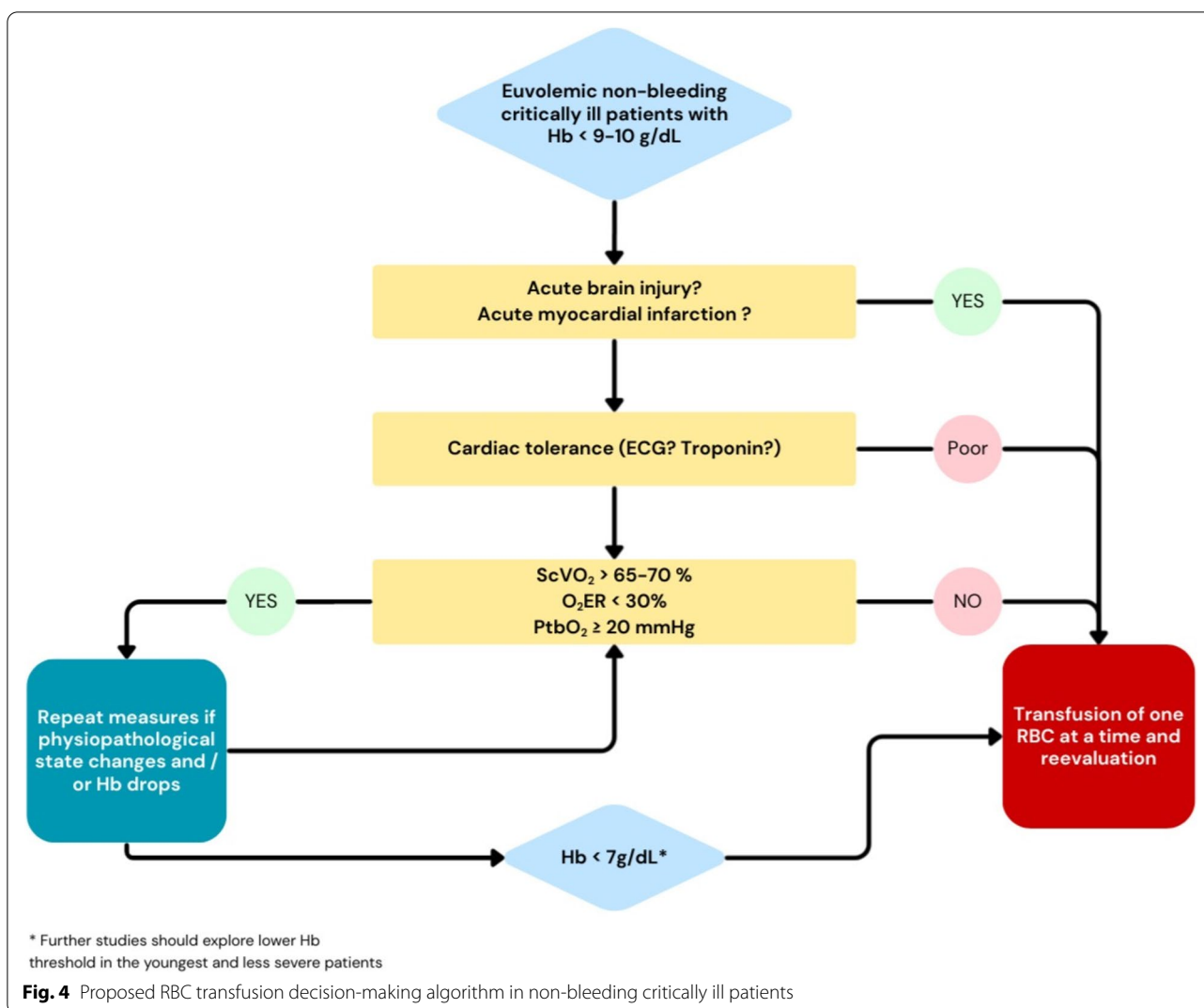
physiological parameter allowing the identification of patients who might benefit from giving or withholding RBC [63].

O₂ER

The ratio of VO₂ to DO₂ defines the O₂ER, the fraction of delivered oxygen that is actually taken up by the tissues [67]. It is calculated as $1-SvO_2/SaO_2$, which are determined from Hb, oxygen saturation, and partial pressure of oxygen. Measurement requires an arterial line for arterial blood sampling and a central venous catheter for central venous sampling. O₂ER serves as a global index of oxygenation, adaptively increasing to meet oxygen demands and maintain a stable VO₂ under normal physiological conditions [68, 69]. In case of anaemia, O₂ER can increase significantly, reaching levels between 40 and 50%, to compensate for the decrease in DO₂ secondary to anaemia [69, 70]. This makes O₂ER a valuable parameter for identifying the restoration of oxygen transport balance following RBC transfusion [71–73].

Several observational studies have analysed the changes in O₂ER after RBC transfusion in different settings (sepsis, post-cardiac surgery, and critical care) [44, 60, 65, 74–77]. They found that RBC transfusion causes a varied effect in O₂ER. Some studies have reported an improvement in O₂ER after RBC transfusion, whilst other studies did not. A meta-analysis including 702 transfusions found a significant decrease in the mean O₂ER of 3.71% (95% CI – 4.44 to – 2.98) after transfusion, suggesting an improvement in the balance between DO₂ and VO₂ in non-bleeding critically ill patients [21]. Other observational studies have evaluated the potential role of O₂ER as a transfusion trigger in the ICU setting. Orlov et al. found that O₂ER decreased in cardiac surgery patients after RBC transfusion mainly in patients with elevated O₂ER (>30%), whilst it did not significantly change in patients with normal values (≤30%) [71]. Moreover, when O₂ER was used with Hb level to guide transfusion, 27 transfusions from 62 (43%) could have been potentially avoided [71]. These data suggest that incorporating O₂ER into the transfusion decision could reduce RBC transfusion.

In a recent observational study, an O₂ER-based “appropriate strategy” (using the median value of 29% for O₂ER) was independently associated with a lower 90-day mortality (OR 0.44 [95% CI 0.23–0.86]; *p*=0.02) in non-bleeding critically ill patients [63]. In this study, O₂ER had a good performance in identifying the correct timing for RBC transfusion, potentially affecting 90-day mortality in non-bleeding critically ill patients [63]. However, no large randomised trials have yet evaluated whether O₂ER-guided transfusion improves outcomes. A randomised clinical trial addressing this question is currently ongoing (NCT06102590).



Arterial lactate

Arterial lactate is a marker of tissue hypoxia, but it is neither specific nor sensitive for it. Significance of an increased arterial lactate level might relate to an unbalance between DO_2 and VO_2 , but also to impairment in O_2 extraction, microcirculation, or mitochondrial function [10, 78]. Lactate production and clearance rely on several elements in critically ill patients, and oxygen delivery is only one of those [10]. As a result, changes in lactate after RBC transfusion in critically ill patients are inconsistent [21, 54]. A meta-analysis including 33 studies did not report any change in lactate after RBC transfusion [21]. These results echoed a physiological study in animal models that did not find an increase in lactate except in pre-mortem animals severely anaemic [79].

Although lactate measurement is simple and commonly performed in routine care in critically ill patients, its use to guide RBC transfusion is not supported by either physiological or clinical evidence.

Troponin

At rest, O_2 extraction in the coronary arteries accounts already for 60% (versus 20–30% for other organs). Therefore, a drop in DO_2 , or an increase in VO_2 , can only be covered by an increase in cardiac output that will lead to a cardiac VO_2 increase. Anaemia has been well identified as a key risk factor for ischaemic cardiac events [80, 81]. However, it remains unknown whether the isolated rise of troponin should be a trigger for RBC transfusion. In the acute geriatric unit, 30-day mortality was higher

in anaemic patients with an isolated high troponin level (<10 g/dL), when compared to anaemic patients with normal troponin. In this study, transfusion did not significantly lower 30-day mortality [82]. Recently, Coz Yataco et al. recommended that in case of isolated elevation of serum troponin without any evidence of cardiac ischaemia, to apply a conservative threshold for RBC transfusion (with a very low certainty of evidence) and to seek additional clinical factors and repeated investigations, including ECG and serum troponin level [83]. Altogether, this evidence does not support the use of isolated increased troponin to initiate RBC transfusion; however, ECG changes and angina clinical symptoms, must be carefully monitored in anaemic patients with a rise in troponin or at risk of myocardial ischaemia.

Tissue perfusion

Microcirculatory dysfunction is common in critically ill patients and plays a key role in the pathogenesis of organ failure during critical illness [84, 85]. Studies using video microscopy techniques have demonstrated that microcirculatory alterations appear early in the course of sepsis [86] and that the severity of these disturbances correlates with patient outcomes [87–89]. Notably, the mechanisms regulating tissue perfusion can become dissociated from global oxygen delivery, resulting in a state of persistent tissue hypoperfusion and microvascular dysfunction, even after normalisation of systemic haemodynamic parameters like SvO_2 , arterial pressure, and CO [85, 90]. Persistent tissue hypoperfusion and microvascular abnormalities despite macrohaemodynamic stabilisation have been associated with ongoing organ dysfunction and increased mortality in critically ill patients [91–93]. Importantly, resolution of microvascular dysfunction following therapeutic interventions has been associated with improved outcomes [94, 95]. Thus, monitoring microcirculatory parameters has been proposed as a more precise and clinically relevant approach than relying solely on macrocirculatory parameters to assess the efficacy of therapeutic interventions in critical illness [96].

RBC transfusion may improve tissue perfusion and oxygenation. However, observational video microscopic studies reported heterogeneous effects of RBC transfusion on microvascular perfusion [44, 97]. In septic and trauma patients, RBC transfusion did not affect sublingual microcirculation assessed by video microscopy, despite increases in Hb, mean arterial pressure, and global DO_2 [44, 98]. However, RBC transfusion improves the sublingual microcirculation in patients with baseline abnormalities, whilst those with normal baseline microcirculation often experience no benefit or even deterioration following transfusion [44, 98]. Similar findings

have been observed using near-infrared spectroscopy (NIRS) to measure muscle oxygen saturation ($NIRVO_2$) and microvascular reactivity, with improvements predominantly seen in patients presenting with baseline abnormalities, whilst those with normal baseline values experienced no change or worsening in tissue oxygenation [97]. Recent studies using skin laser Doppler (SLD) technique showed that the effects of RBC transfusion on skin blood flow (SBF), which is a proxy of tissue oxygen delivery, varied; improvements in SBF were found mainly in patients with low SBF at baseline and no correlation was found between SBF changes and systemic variables after transfusion [99, 100]. Notably, improvements in SBF after RBCT were independently associated with a reduction in organ dysfunction within 24 h after RBCT, suggesting that transfusion might enhance tissue perfusion and support organ function in non-bleeding critically ill patients [100].

PbtO₂

Anaemia is common in patients with acute brain injury and has been associated with secondary brain assault due to reduced CaO_2 and cerebral DO_2 , as well as with poorer clinical outcomes [101, 102]. The physiological response to anaemia may be impaired in this population, as cardiovascular and cardiac function can limit compensatory increases in cerebral DO_2 [103, 104]. Additionally, impaired cerebral blood flow (CBF) autoregulation compromises the brain's ability to vasodilate in response to anaemia, reaching maximal vasodilation at moderate Hb levels (8–9 g/dL) [105, 106]. Therefore, Hb alone is insufficient to assess cerebral hypoxia [106]. Maintaining adequate cerebral oxygenation is feasible in clinical practice and may be particularly useful for guiding transfusion strategies [107, 108]. Brain tissue oxygenation partial pressure (PbtO₂) reflects a dynamic balance between DO_2 , oxygen diffusion, oxygen consumption, and oxygen extraction, and is measured via an invasive probe placed in the subcortical white matter [109]. The most common threshold used to define brain tissue hypoxia is a PbtO₂ <20 mmHg [108].

Clinical studies supports the relevance of PbtO₂ monitoring. In patients with acute brain injury, anaemia (Hb <9 g/dL) and low levels of brain tissue oxygenation (PbtO₂) but not anaemia alone was associated with a higher risk of unfavourable outcomes [110]. Moreover, the reported effects of RBC transfusion on PbtO₂ are inconsistent; with an increased brain oxygenation in some patients [110] and a drop in others [111]. Recently, Gouvea-Bogossian et al. conducted a study to assess the predictors of such response; they found that lower baseline PbtO₂ but not baseline Hb was a strong predictor of

a significant increase in PbtO_2 after RBC transfusion in patients with acute brain injury [112].

Perspectives

There is a need for further research to assess whether guiding RBC transfusion by macrocirculatory parameters, such as ScvO_2 and O_2ER , impact on patients' prognosis and RBC transfusion requirements. Additionally, studies are necessary to identify reliable microcirculatory markers that reflect impaired tissue oxygen delivery and that could potentially be used to guide transfusion decisions. Furthermore, whilst RBC transfusion may enhance tissue perfusion by increasing arterial oxygen content, it can also rise cardiac output through volume effects; as such, combining tissue perfusion parameters with haemodynamic measurements could clarify whether tissue perfusion changes reflect improved arterial oxygen content or simply improved preload. This research should focus on specific subgroups of patients. For instance, investigating the benefit of integrating impaired cerebral oxygenation and neuromonitoring in the transfusion decision-making process on the prognosis of patients with acute brain injury is warranted. In this context, Fig. 4 illustrates our original physiologic framework for guiding RBC transfusion. Such algorithm requires validation by further research. In addition, research investigating how and whether these physiologic parameters could be used in actively bleeding patients should be conducted. Also, the question of the routine implementation of such practice should also be addressed especially in countries with limited resources. Finally, measures of physiological triggers require invasive central lines and arterial catheters; their used might be challenged by a trend for less-invasive approaches [113].

Conclusions

In euvoletic, anaemic patients, transfusion decisions should move beyond haemoglobin thresholds alone, incorporating individualised triggers that reflect anaemia tolerance—particularly cardiac tolerance. A multimodal strategy, including clinical signs, ECG changes, biochemical markers, and microcirculatory assessment, may optimise transfusion timing and avoid unnecessary red blood cell administration. However, current evidence remains insufficient to support routine integration of oxygenation reserve surrogates, such as ScvO_2 and O_2ER into transfusion protocols. Further research is needed to determine whether targeting tissue oxygenation or microcirculatory parameters during RBC transfusion improves clinical outcomes across diverse patient populations.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-026-08304-w>.

Abbreviations

ICU: Intensive care unit; ScvO_2 : Central venous oxygen saturation; Hb: Haemoglobin; A-VdiffO_2 : Arterial–venous oxygen difference; O_2ER : O_2 extraction ratio; PtbO_2 : Brain tissue oxygenation partial pressure; SvO_2 : Venous oxygen saturation; DO_2 : Oxygen delivery; VO_2 : Oxygen consumption.

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Author contributions

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Conflicts of interest

CA performed lectures for Cerus, VIFOR CSL, and MSD.

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Consent for publication

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